Editorial

Immune Escape Mechanisms in Non-Small Cell Lung Cancer: From Biological Complexity to Actionable Targets

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ABSTRACT: Despite significant progress in immune checkpoint inhibitors (ICIs) and targeted therapies, non-small cell lung cancer (NSCLC) continues to be associated with high rates of primary and acquired resistance. Although PD-1/PD-L1 blockade has revolutionized treatment, its clinical development has largely followed a one-size-fits-all approach, relying on limited biomarkers such as PD-L1 expression or tumor mutational burden. It is now increasingly clear that immune escape in NSCLC is orchestrated by a multifaceted, multilayered network of both tumor-intrinsic alterations and TME (tumor microenvironment)–driven mechanisms. The challenge has been to understand and to therapeutically exploit these immune escape pathways and this knowledge is now needed so that rather than embark on empirical combinations we can advance to rational, immune-informed targeted therapies.

1. Tumor-Intrinsic Drivers of Immune Escape

Somatic aberrations in tumor cells drive antitumor immunity. In particular, loss-of-function mutations in STK11/LKB1 and KEAP1 have come to be considered paradigmatic immune-cold drivers in NSCLC. Defective T-cell infiltration, dysfunction instead of activation of the interferon signaling, and resistance to PD-1 blockade despite the presence of PD-L1 expression has been documented after STK11 mutation associated with deficiency in other tumor types [1,2]. In a similar fashion, KEAP1 mutations drive metabolic remodeling and resistance to oxidative stress creating an immunosuppressive environment that also correlates with poor response to immunotherapy [3].

Another tumor-intrinsic immune exclusion mechanism that is represented by activation of the WNT/β-catenin pathway which promotes defective dendritic cell recruitment and impaired T-cell priming [4]. Simultaneously, changes in antigen presentation machinery such as HLA class I loss, β2-microglobulin mutations and interferon-γ signaling defects directly impair immune recognition, further facilitating immune evasion following therapeutic selection pressure [5].

Recent evidence has further refined this concept by demonstrating that immune escape in NSCLC is often subclonal rather than uniform. High-resolution analyses revealed that distinct tumor subclones may independently acquire immune-evasive features, resulting in spatially heterogeneous immune pressure and mixed clinical responses to ICIs [6]. These findings provide a biological explanation for early resistance and highlight the limitations of single-biopsy–based biomarkers.

These molecular characteristics not only emphasize the reason PD-L1 expression cannot fully characterize the immunological complexity in NSCLC but point to the necessity of integrating tumor genomics into ongoing therapeutic approaches targeting immunity.

2. The Tumor Microenvironment as an Active Driver of Resistance

Apart from mechanisms aimed at cancer cell–intrinsic escape, immune evasion in NSCLC is heavily influenced by the TME. Tumor-associated macrophages (TAMs), especially the ones polarized toward an M2-like phenotype, inhibit cytotoxic T-cell activity by producing IL-10, TGF-β and arginase, and promote tumor angiogenesis and progression [7]. Similarly, regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) inhibit effector immune responses in actively way and are associated with resistance to ICIs [8].

Cancer-associated fibroblasts (CAFs) also facilitate immune evasion by undergoing changes that remodel the extracellular matrix and lead to mechanical barriers to immune infiltration, as well as secreting immunosuppressive cytokines [9]. This leads to an overall spatial and functional heterogenity of the immune miocroenvironment that complicates the success of immune checkpoint blockade and mandate therapeutic strategies that directly address this stroma and myeloid components.

3. Metabolic and Signaling Pathways as Immune Targets

New emerging data demonstrates the role of metabolic immune escape mechanisms in NSCLC. Accumulation of adenosine in the TME due to CD39 and CD73 activity inhibits T-cell and natural killer cell activity through A2A receptor signaling and is viewed as a potential therapeutic target [10]. Dysregulated tryptophan metabolic pathway through indoleamine 2,3-dioxygenase (IDO) is associated to T-cell exhaustion and immune tolerance as well [11].

Importantly, the TGF-β pathway is at the juncture of immune suppression and tumor progression, contributing to T-cell exclusion, CAF activation and epithelial–mesenchymal transition. The clinical failures of unselected TGF-β inhibition highlight the need for biomarker-driven strategies that prioritize individuals most likely to respond to targeting this pathway [12].

4. Rethinking Targeted Therapy in the Immunotherapy Era

This limited success of combining ICIs with conventional targeted therapies in oncogene addicted NSCLC is one of the most critical problems, as most of the targeted agents were developed without contemplating the immunological implications of their use. Indeed, EGFR- and ALK-driven tumors, for example, show low levels of tumor mutational burden, defective antigen presentation, and immunosuppressive TMEs that likely explains their lack of responsiveness to immunotherapy [13,14].

Rather than pursuing unselected combinations, future strategies should focus on targeting immune escape mechanisms themselves. Insights from other immunotherapeutic platforms, including adoptive cell therapies, further emphasize the dominant role of the microenvironment in shaping resistance, with shared suppressive circuits involving myeloid cells, stromal barriers, and metabolic competition [15].

In this context, the concept of targeted therapy warrants redefinition. No longer confined to inhibition of oncogenic drivers, targeted therapy in the immunotherapy era should encompass interventions aimed at specific immune-evasive pathways that actively shape tumor–immune interactions.

Future strategies should instead aim to target mechanisms of immune escape themselves, rather than randomly chasing unselected combinations. Such therapies may involve myeloid cell modulation, tumor metabolic reprogramming, restoration of antigen presentation and converting immune-cold tumors to immune-inflamed tumors.

5. Toward Immune-Informed Targeted Therapies

Molecular mechanisms underpinning immune escape in NSCLC need a paradigm shift. We should really think about targeted therapy not simply as an inhibition of oncogenic drivers, but also as a re-adaptation of tumor–immune interactions. For the identification of opportunistic immune-evasive mechanisms and rational topping up strategies, molecular profiling merged with immune characterization will be relevant.

Eventually, the future of precision oncology in NSCLC will require targeting not only the tumor genome, but also the immune pathways that allow cancer and resistance to treatment to persist.

Ultimately, abandoning the one-size-fits-all immunotherapy paradigm in favor of immune-informed targeted approaches may represent the most critical step toward achieving durable clinical benefit in NSCLC.

Author Contributions

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